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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,541	ESHLEMAN ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,23,28-30,40-42,75 and 76* is/are pending in the application.

4a) Of the above claim(s) *1-5,23,28-30,40-42,75 and 76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-15, 23, 28-30, 40-42, 75 and 76 are pending.

Claims 1-5, 23, 28-30, 40-42, 75 and 76 are withdrawn from examination as detailed below.

Claims 6-15 are examined on the merits.

Election/Restrictions

1. Applicant's election without traverse of the invention of Group 1 (claim 6-13, and linking claims 14 and 15) in the reply filed on 09/26/2008 is acknowledged. Applicants' further election of the particular KRAS2 mutations of G35A, relevant to the recitations in claim 8, is also acknowledged.

Claims 1-5, 23, 28-30, 40-42, 75 and 76 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 09/26/2008.

Claim Objections

2. Claim 8 is objected to because of the recitation of non-elected subject material in the alternative. Applicants have elected for the examination of claims in so far as they require the specific KRAS2 mutation 'G35A'. No claim is yet indicated allowable. Prior to the allowance of the objected to claim, if non-elected subject matter is not rejoined, the non-elected subject matter will be required to be deleted from the claim.

Objection to the Specification - Sequence Compliance

4. This application (10/590,541) contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 at least for the reason(s) set forth below:

Throughout the specification (see for example: pages 67, 76-80, 98, 99, 108; and Figures 5, 16, 22 and 23) the application recites nucleic acid sequences that are not identified by any SEQ ID NO: sequence identifier, and are not presented in any Sequence Listing included with the application.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must provide a paper copy of a Sequence Listing, a computer readable form (CRF) of the Sequence Listing, a statement indicating that the paper copy and CRF are the same, and a statement directing the entry of the Sequence Listing into the instant specification. The specification must be amended to properly identify any sequences in the text of the specification (including appropriate identification by SEQ ID NO: of any sequences in any figures in the brief description of the figures) using the using the identifier "SEQ ID NO:" from the Sequence Listing. Applicants shall indicate where in the priority documents as originally filed (provisional applications 60/555,167 and 60/619,817) such sequences are presented.

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 6-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-10 and 13 are unclear over the stated purpose of the claimed methods as 'differentiating pancreatic cancer from chronic pancreatitis', as recited in the preamble of independent claim 6. The claimed methods comprise the steps of contacting a nucleic acid sample with oligonucleotides, ligating, and amplifying, where such method steps do no result in 'differentiating pancreatic cancer from chronic pancreatitis'. It is thus unclear how the method steps of the claim accomplish the purpose of claimed method.

Claims 6-13 and 14-15 are unclear over recitation of the limitation of 'either P1 or P2 comprise a nucleotide difference' (as recited in claim 6 and claim 14) because it is unclear what the nucleotide of P1 or P2 is required to be different from. The claim does not set forth any standard to which the nucleotide of P1 or P2 is compared to determine that there is a 'nucleotide difference'.

Claims 7 and 8 are unclear over recitation of the limitation that 'the nucleotide difference is in KRAS2', as recited in claim 7. The independent claim requires that one

of the oligonucleotides of the oligonucleotide pair has a nucleotide difference, thus it is unclear how the nucleotide difference, required to be in P1 or P2, is in KRAS2.

Claim 8 is unclear over recitation of the requirement that a nucleotide difference is G35A. The claim does not offer a specifically limiting definition as to what is required for a G35A nucleotide difference. As such, the metes and bounds of the structural limitations of the claimed method is unclear.

Claims 11 and 12 are unclear over recitation of the limitations in each claim 'wherein a mutation level' of a particular range is indicative of chronic pancreatitis (claim 11) or pancreatic cancer (claim 12). There is no requirement in either the rejected claims or the independent claim from which the rejected claims depend for the identification of any 'mutation level'. As such there is a lack of proper antecedent basis for the limitation, and the requirements of the claimed method are unclear.

Claims 14 and 15 are unclear over the stated purpose of the claimed methods as 'diagnosing a disease in a subject', as recited in the preamble of independent claim 14. The claimed methods comprise the steps of contacting a nucleic acid sample with oligonucleotides, ligating, and amplifying, where such method steps do no result in 'diagnosing a disease in a subject'. It is thus unclear how the method steps of the claims accomplish the purpose of claimed method.

Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 6-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

> A method of differentiating pancreatic cancer from chronic pancreatitis in a human subject, said method comprising:
> obtaining a biological sample from said human subject, said sample comprising nucleic acids from said subject;
> hybridizing said nucleic acids with at least one oligonucleotide pair to form a reaction mixture; wherein said oligonucleotide pair comprises a first oligonucleotide and a second oligonucleotide; wherein said first oligonucleotide comprises a first gene specific region and a first primer region, and said second oligonucleotide comprises a second gene specific region and a second primer region; wherein either said first oligonucleotide or said second oligonucleotide specifically hybridizes to the nucleotide sequence encoding the A allele of the G35A nucleotide mutation in the KRAS2 gene, said G35A nucleotide mutation encoding the G12D KRAS2 amino acid substitution; and wherein said first oligonucleotide said second oligonucleotide are suitable for ligation to one another;
> subjecting the reaction mixture to a ligation reaction to form a ligation product;
> amplifying said ligation product to form a reaction product;
> detecting said reaction product, wherein detecting said reaction product indicates the presence of said A allele of the G35A nucleotide mutation in the KRAS2 gene in said nucleic acids from said subject;
> wherein the presence of said A allele of the G35A nucleotide mutation in the KRAS2 gene in said nucleic acids from said subject is indicative of an increased likelihood of the presence of pancreatic cancer in said subject.

does not reasonably provide enablement for the breadth of the method as claimed which encompasses analysis of samples in any subject organism, and the detection of any mutations in any gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims are drawn to methods of differentiating pancreatic cancer from chronic pancreatitis using a particular amplification methodology to detect nucleotide content.

The claims encompass the analysis of any subject organisms.

The claims encompass the analysis of any nucleotide content in any gene.

The invention thus requires knowledge of a correlative association between a wide variety of nucleic acid content in any organism and the presence of either pancreatic cancer or chronic pancreatitis.

Direction provided by the specification and working example

The instant specification provides examples (e.g. pages 76-91) of the analysis of KRAS2 mutations in human patients with either pancreatic cancer on non-cancerous pancreatic disorders. The specification provides, consonant with the election, the analysis of (see for example p.12 p.89) a specific KRAS2 gene mutation identified as G35A (a G to A mutation at position 35, where the A of the initiator ATG is position 1) which changes codon 12 from GGT to GAT, changing amino acid 12 from glycine to aspartic acid (this nucleotide mutation is known in the art as the G12D mutation). The specification provides that the presence of the G12D encoding mutation is indicative of pancreatic cancer as opposed to benign disease (for example Table 4, p.91).

The specification does not provide for the generic association of any mutation in any gene with the presence of pancreatic cancer or any other pancreatic disorder; nor does the specification provide for any nucleotide content (other than the G12D mutation) as a G35A mutation.

The specification does not provide for any analysis of any non-human subjects.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art in detecting variable nucleotide content at any known mutation hot spot is high, the unpredictability in associating any nucleotide content with any particular phenotype, or extrapolating variable nucleotide content from any one organism to any other different organism is higher. The high level of unpredictability is demonstrated by the prior art.

The claims encompass the analysis of any nucleotide position and any nucleotide content, and recite only the term 'G35A' with regard to any specific mutation, and because the claims encompass any subject organism The specification teaches only the analysis of (as consonant with the Election) a specific KRAS2 gene mutation identified as G35A (a G to A mutation at position 35, where the A of the initiator ATG is position 1) which changes codon 12 from GGT to GAT, changing amino acid 12 from glycine to aspartic acid (this nucleotide mutation is known in the art as the G12D mutation) in human subject.

It is thus relevant to point out the unpredictability in extrapolating the presence of polymorphic nucleotide content, or its association with any phenotype, form one animal to any other different animal. Such unpredictability in interspecies extrapolation is addressed by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

Additionally, Hacker et al (1997) teaches that they were unable to confirm an association between particular variable nucleotide content and a phenotype (i.e. the phenotype of ulcerative colitis) in a case where prior studies suggested such a

relationship would exist since the relationship had been identified in a different population (pages 623-627). Thus it is highly unpredictable as to whether or not the analysis of any nucleotide content, as encompassed by the specification, would be reliably associated with either pancreatic cancer or chronic pancreatitis.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention in the full scope of the claims. Within the scope of the claimed invention one would have to perform experimentation to identify in any non-non human subjects any nucleic acid content that is particularly indicative of either pancreatic cancer or chronic pancreatitis. Even if one were to perform such experimentation, there is no assurance that any other reliable associations, beyond those identified earlier in this rejection (i.e. as consonant with the election, a specific KRAS2 gene mutation identified as G35A (a G to A mutation at position 35, where the A of the initiator ATG is position 1) which changes codon 12 from GGT to GAT, changing amino acid 12 from glycine to aspartic acid) as enabled by the instant specification would be found.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the specific working examples, it is the conclusion the an undue amount of experimentation

would be required to make and use the claimed invention in the full scope as encompassed by the claims.

Claim Rejections - 35 USC § 102

In the rejection of claims under 35 USC 102 as anticipated by the prior art it is noted that the recitation of the intended use of the claimed method, as stated in the preamble of the independent claims, is not given patentable weight in differentiating the claimed methods from the methods taught by the prior art. See MPEP 2111.02, part II "where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation".

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 6, 9, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Schouten et al (2002) as cited on the IDS of 08/25/2006.

Schouten et al teaches a method comprising all of the method steps recited in independent claims 6 and 14. The method of Schouten et al (summarized in Fig.2 on p.4, and Fig 8 on p.11) comprises contacting a nucleic acid sample with a pair of oligonucleotides in which each of the oligonucleotides has a gene specific region (termed 'hybridisation sequence' in the reference) and a primer region (termed 'PCR

primer sequence Y' and 'PCR primer sequence X' in the reference). The reference indicates that mutation detection can be accomplished by using a nucleotide difference (as compared to the target nucleic acid sequence) in the gene specific region of one oligonucleotide (p.11, right col., lns.5-10). The method steps of the reference indicate that the primers of the pair are suitable for ligation to one another (p.2, right col., ln.1). Furthermore the reference teaches a ligation reaction and amplification of the formed ligation product (p.2, right col., ln.1-23).

Regarding claim 9, the reference teaches analyzing the reaction product (Fig 3).

Regarding claim15, the limitations of claim 15 only effect he preamble to the method of the independent claim. As such the method steps of the dependent claim are the same as the methods steps of the independent claim, which are satisfied by the teachings of the prior art reference as detailed earlier in this rejection.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 7, 8, 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over et al (2002), as cited on the IDS of 08/25/2006, in view of Maire et al (2002) and Lecomte (2002).

Schouten et al teaches methods of nucleic acid sequence analysis comprising all of the method steps recited in independent claim 6, from which the rejected claims depend.

Schouten et al does not specify the analysis of KRAS mutations (claims 7, 8, 10 and 13), nor mutations indicative of a phenotype (claim 11 and 12).

However, the analysis of a G35A mutation in KRAS2 and its association with pancreatic cancer was well known in the art at the time the invention was made.

Maire et al teaches the analysis of mutations in differentiating between pancreatic cancer and chronic pancreatitis.

Relevant to claims 7, 8, 10, and 13, Maire et al teaches the analysis of G12D mutations in codon 12 of the KRAS2 gene (p.552 – Detection of KRAS2 gene mutations) (relevant to the requirements of claims 7 and 8). Relevant to the limitations of claim 8, as consonant with the Election, the mutation analyzed by the allele specific amplification of Maire et al is the same G35A mutation of the instant specification, as evidenced by Lecomte et al (Table 1). Relevant to claims 10 and 13, the analysis of allele specific amplification products is determining a KRAS mutation level (relevant to claim 10) and analysis of mutations in subjects is monitoring KRAS mutation levels (relevant to claim 13).

Relevant to the limitations of claims 11 and 12, Maire et al teaches that the presence of the KRAS2 G35A mutation is indicative of pancreatic cancer as opposed to chronic pancreatitis (p.552 – KRAS2 mutations in circulating DNA; p.551 - Abstract). It is noted that the required limitations of the rejected claims (i.e. 'a mutation level') has been addressed previously in this Office Action under 35 USC 112 2nd ¶). However, the teaching of Maire et al, with regard to limitations of the claims, indicate that a mutation level of 0.0% (e.g. undetected KRAS2 mutation) is indicative of chronic pancreatitis (claim 11), and a mutation level of 100% (e.g. KRAS2 mutation detected in all samples from a subject) is indicative of pancreatic cancer (claim 12).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Schouten et al for the analysis of the KRAS2 G12D mutation as taught by Maire et al to be indicative of the presence of pancreatic cancer. One would have been motivated to analyze the mutation of Maire et

al based on the assertion of Maire et al that such an analysis is useful as a cancer diagnostic (p.553, right col., last paragraph).

Conclusion

13. No claim is allowed. No claim is free of the teachings of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
Art Unit 1634